FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
May 12, 2010
NDA 22478, Naproxcinod

Questions to the Committee

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1. Based on the results of the studies assessing the efficacy of naproxcinod and naproxen:

    a. Is there evidence that naproxcinod is as effective as naproxen?

    b. Is the applicant's choice of a noninferiority margin of 70% of the treatment effect size appropriate to determine that efficacy of the two products is similar?

        i. If not, what would be an acceptable noninferiority margin for this situation?

    c. Do you think that the reduced relative bioavailability may have been a factor in failure to demonstrate noninferiority?

2. The data presented demonstrate that there is an average difference in blood pressure measurements, but no sustained effect throughout the dosing interval. Discuss whether the blood pressure effects of naproxcinod are likely to improve cardiovascular outcomes in patients requiring long-term treatment with naproxen.

    a. Will the lack of sustained effect throughout the dosing interval result in a failure to reduce the risk for adverse cardiovascular outcomes?

    b. Does the peak effect on blood pressure pose a potential safety concern for patients?

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3. The data presented describe an effect on the occurrence of erosions, but were not of adequate design to assess an effect on the occurrence of ulcers. Discuss whether the effects of naproxcinod to reduce the number of erosions in the absence of demonstrating an effect on gastric ulcers has clinical value in patients requiring long-term treatment with naproxen.

    a. Are the studies submitted adequate to assess whether there is a meaningful effect on GI outcomes?

    b. If not, what changes should be made for future studies?

    c. Can the effect on GI outcomes be explained by the lower relative exposure to naproxen that result from dosing with naproxcinod?

4. Please vote on whether naproxcinod should be approved for the indication of the treatment of the signs and symptoms of osteoarthritis, taking into account the efficacy, pharmacokinetic and safety findings. (YES/NO/ABSTAIN)